RESCINNAMINE IN TREATMENT OF HYPERTENSION IN HOSPITAL CLINIC AND IN GENERAL PRACTICE*

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Preparations of *Rauwolfia serpentina*, and in particular its alkaloid reserpine, are widely used in the treatment of hypertension. Their value has been challenged on the grounds that they rarely produce an adequate result in severe hypertension and that they can cause undesirable side-effects, especially depression.

Many workers feel that they still have a place in the management of less severe hypertension, and that the adoption of smaller dosage reduces significantly the risk of side-effects. It has been suggested that rescinnamine, another alkaloid of rauwolfia, might have an antihypertensive effect equal to that of reserpine, but with less tendency to cause depression.

The following report describes an experiment with two objectives: firstly, to determine whether the antihypertensive effect of reserpine on a group of patients might be equalled by a smaller dose of reserpine together with rescinnamine, and whether the combined regime might have fewer side-effects; and, secondly, to compare the conclusions of the hospital clinic with an independent assessment of the results in the same patients by their own family doctors, during the same period of time.

It was hoped also to obtain some data about the relationship between blood-pressure readings made in the hospital clinic and those made in the home or in the consulting-room.

Material and Methods

Nine general practitioners were invited to co-operate in this investigation. They were asked to select a few of their patients with moderate hypertension who might benefit from antihypertensive therapy and who would be able and willing to attend at regular intervals over a period of nine months. No strict limitations were applied to the choice of patients, but it was suggested that their "casual reading" at the time of selection should be not less than 180/100 mm. Hg, and that those with very severe hypertension should not be included because the design of the experiment required prolonged mild antihypertensive therapy, unlikely to be sufficient for them. By the criterion of greater severity used in previous publications from this department (Fife *et al.*, 1958, 1959)—namely, a mean diastolic pressure while on placebo therapy of 120 mm. Hg or over—only 4 of the 23 patients finally included would be regarded as severe cases; 16 were "milder" cases, and 3 would have been omitted as "too mild" because their mean diastolic pressure on placebo was under 100 mm. Hg.

The ages ranged from 47 to 72 years, with an average of 58. All but one were women. On an average they were thus older and had less severe hypertension than the groups of hypertensives previously studied by this unit.

The initial assessment included 12-lead electrocardiogram, radioscopy, and blood-urea estimation, and, in patients under 55 years of age, intravenous pyelography. By the usual criteria, all were considered to have hypertension of idiopathic type.

The patients attended hospital once a month at a time set aside for this purpose, and the general practitioners, so far as was possible, attended with their own patients and participated actively in the assessments and observations. Between the hospital visits the patients were attended by their own doctors weekly, and two independent records of blood-pressure readings were kept, one in the hospital clinic and the other for readings made at home or in the consulting-room.

The clinic blood-pressure readings consisted of six measurements at each visit, the first in the sitting position, the second and third in the recumbent position at 15 and 30 minutes respectively, and the last three at one-minute intervals in the standing position. The "home" or "consulting-room" readings consisted of two measurements at each visit, one in the recumbent position and one standing.

Therapy

The treatment consisted of three consecutive three-month courses of tablets, requiring a total attendance by each patient of nine months. The tablets were supplied in bottles labelled Regime 1, 2, and 3 respectively, and neither the patients nor the doctors knew which was which. One day's supply of the various regimes was as follows:

Regime 1: Reserpine 0.5 mg. + rescinnamine 1 mg.
Regime 2: Reserpine 1.5 mg.
Regime 3: Placebo.

Thirty-five patients began this experiment, but for various reasons 14 were excluded before it was completed. In order to avoid possible bias from the order in which the regimes were used, successive patients began with a different regime, so that approximately one-third of the patients had each of the regimes as their first.

In terms of the clinic blood-pressure readings, the result of a regime of therapy was calculated by subtracting the mean of the three sets of six readings made during that therapy from the corresponding mean pressure while on the placebo. Both systolic and diastolic pressures were examined, and the pressure reduction was calculated as a percentage of the placebo mean pressure.

TABLE I.—*Percentage Reduction in Systolic and Diastolic Pressures from the Two "Active" Regimes*

Percentage Reduction	Systolic				Diastolic			
	Regime 1		Regime 2		Regime 1		Regime 2	
	Clinic	Home	Clinic	Home	Clinic	Home	Clinic	Home
0–5	4	3	11	7	7	4	7	3
6–10	4	4	2	5	4	5	5	8
11–15	3	2	2	3	5	5	4	3
16–20	1	1	1	1	2	1	4	4
21–25	0	0	0	0	0	0	0	1
Rise in pressure	9	10	5	4	3	5	1	1
Total patients ..	21	20*	21	20*	21	20*	21	20*

* Home record of one patient inadequate—excluded.

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To represent the home or consulting-room blood-pressure we had available for each regime of treatment from 8 to 12 sets of two blood-pressure readings; the average of all of these was taken, except for readings made within two weeks of commencing a new regime. The fall in pressure from the placebo level was calculated in the same way as for the clinic readings.

The reductions in pressure are summarized in Table I. If the clinic assessment is considered first, it is seen that the mild antihypertensive effect of reserpine in a dose of 1.5 mg. daily is again confirmed, and that this effect is greater on the diastolic pressure than on the systolic. Four of the 21 patients had a fall in mean diastolic pressure of 16% or more, but only one achieved such a fall in systolic pressure.

The combination of reserpine 0.5 mg. and rescinnamine 1 mg. daily appeared to be slightly less effective than reserpine 1.5 mg. daily; indeed, in the case of the systolic pressure there was a rise in almost as many patients as there was a fall. The effect of this combination of drugs on the diastolic pressure was a little more convincing, but in only 2 of the 21 patients was the pressure reduction 16% or over, which one might reasonably require for a "clinically useful" response.

Turning now to the home or consulting-room results, we see that very similar conclusions may be reached from them. Five of 20 patients had a fall in diastolic pressure on reserpine alone of 16% or over, as compared with one patient on the combined regime. The effects on systolic pressure were again of less degree, and only one patient had a clinically useful reduction of systolic pressure from each regime.

In brief, the results of both assessments suggest that a combination of reserpine 0.5 mg. daily and rescinnamine 1 mg. daily has a mild antihypertensive action similar to but probably less than that of reserpine alone in a dose of 1.5 mg. daily.

It is important to know also whether the combined regime had a lower toxicity than reserpine alone. The difficulty of ascertaining that in clinical trials of this type is shown in Table II, which lists the frequency of

TABLE II.—*Symptoms Complained of During the Three Regimes*

Symptom	Regime 1	Regime 2	Regime 3
Tiredness, lethargy	5	9	5
Drowsiness	1	4	
Depression	1	3	6
Nervousness		4	5
Weakness	1		
Insomnia		1	1
Dyspepsia, nausea	2	1	1
Headache	2	1	6
Lightheadedness	4		
Chest pain	3	3	3
Dyspnoea		2	
Palpitation			1
Salty taste		1	1

symptoms complained of while on the various regimes, including the placebo, whether these were thought to arise from the drugs or not. The rather high incidence of a number of symptoms, such as depression, nervousness, and tiredness, during the placebo regime suggests that one should be cautious about making too many deductions about the effect of the active drugs in producing these symptoms. One might be justified in thinking, however, that the bigger dose of reserpine had a greater tendency to produce sleepiness or lethargy than the smaller dose of reserpine along with rescinnamine. The frequency of depression during the placebo regime in the present series makes it impossible to draw any valid conclusions about the relative merits of the other two regimes in terms of this side-effect.

Discussion

While preparations of *Rauwolfia serpentina* are in common use in the clinical management of hypertension, their value, particularly in severe hypertension, has been questioned (Turner, 1959). The alkaloid reserpine, which has had the widest use, is known to produce depression as a side-effect in a proportion of cases, and although this is less often seen with the smaller dosages now favoured for its use in hypertension, the depression may occasionally be severe. Numerous other alkaloids of rauwolfia have been isolated and several are now in clinical use.

Rescinnamine was isolated and identified chemically by Klohs *et al.* (1954), and its pharmacology was described by Cronheim *et al.* (1954). Its hypotensive effect in dogs was found by Cronheim and Toekes (1955) to be greater than that of reserpine. From a clinical trial in human hypertension, Smirk and McQueen (1955) reported that there was no important difference between the hypotensive effects of rescinnamine and those of reserpine. They found that certain mental symptoms, such as depression, occurring during reserpine therapy might often by relieved by changing to rescinnamine; but other patients complained of tenseness, anorexia, and abdominal discomfort from rescinnamine. Smirk and McQueen used reserpine in a dose of 0.5 to 1.5 mg. a day, and rescinnamine in the same dosage; and they noted that some patients could tolerate a much larger dose of rescinnamine. Moyer *et al.* (1955) found that rescinnamine in a dose of 2–4 mg. daily was as effective in the reduction of blood-pressure as reserpine, though sometimes less severe; and the findings of Herschberger *et al.* (1956) and of Winton (1957) were essentially similar. On the other hand, Lemieux *et al.* (1956) found that on a weight-for-weight basis rescinnamine was a less potent alkaloid than reserpine, and that a dose of 1–2 mg. daily did not have a significant antihypertensive effect.

Our own results suggest that the antihypertensive effect of rescinnamine 1 mg. daily along with reserpine 0.5 mg. daily is similar to that of reserpine 1.5 mg. daily in respect of a greater effect on diastolic than on systolic pressure, but that it is less in degree than that of reserpine alone in a dose of 1.5 mg. daily. This agrees with the view of Lemieux *et al.*, that, dose for dose, rescinnamine is less potent than reserpine in the therapy of human hypertension.

As regards side-effects, our results were consistent with the view that, in the same dosage, rescinnamine may be slightly less toxic than reserpine, but, in view of the high incidence of similar symptoms in this group of patients while having the placebo, we cannot comment in more definite terms on that aspect.

The evidence of this experiment does not suggest that rescinnamine is likely to offer any substantial advantage over reserpine in the treatment of hypertension.

Collaboration with Family Doctors

It has long been taught that general practice is a fertile field for clinical observation and research. The increasing specialization in hospital practice, and the growth of elaborate techniques of investigation, have perhaps tended to discourage attempts at fundamental

research in general practice, and shortage of time and other factors make even simple clinical investigations difficult to undertake.

In recent years Mackintosh (1954), Fry (1958), and other writers have felt that co-operation between hospital out-patient departments and family doctors should make possible certain types of clinical investigation that would be difficult for either to accomplish alone.

One field in which a combined approach seems worth considering is the clinical assessment of some of the numerous new drugs now available. There are many difficulties in the way of a controlled clinical trial of a drug in general practice. Ethical considerations are involved, and our experience is that patients are more willing, and even keen, to participate in an experiment involving new remedies when it is carried out under the guidance of a hospital clinic with special experience in that field. On the other hand, it is desirable of most remedies that they should be effective and practicable for use in general practice, and it would be helpful if methods of assessment could be devised which were known to give similar results under hospital and general practice conditions.

It is perhaps unnecessary to emphasize that such investigations must be planned in detail in advance, and that a certain sacrifice of time by the participants is inevitable. Where subjective responses of patients are being assessed, or where objective changes of minor degree may be significant, current practice demands that bias of both patient and physician be minimized by the use of the double-blind technique.

This paper describes a simultaneous controlled clinical trial in the hospital out-patient department and in general practice of the effect of certain regimes of treatment for hypertension. On the whole the results of the two assessments show a remarkable agreement.

The tabulated blood-pressure readings were studied to find whether there was any general trend to higher readings in one or other assessment. There is no doubt that a single estimation of blood-pressure at a diagnostic consultation in hospital often gives a much higher reading than the usual level recorded by the family doctor. Yet in this investigation the blood-pressure readings during placebo therapy did not show any general tendency to higher readings at hospital.

In a few subjects there was a substantial and consistent discrepancy between the two sets of readings —for example, Case 5 showed much higher readings in hospital throughout the whole period, and Cases 8 and 15 the converse, particularly for systolic pressure. These facts, and the rather wide scatter of individual readings, indicate once more the need for a fairly large number of blood-pressure recordings in each phase of such an investigation. And it is clear that a smaller number of patients would be unlikely to give a conclusive result.

Simple investigations of this kind, involving close co-operation between hospital and family doctors, can be educative to both and may produce useful information.

Summary

A controlled clinical trial is described comparing reserpine with a smaller dose of reserpine plus rescinnamine in hypertension.

The results were assessed independently at the hospital clinic and by the patients' family doctors, working in co-operation.

Rescinnamine is unlikely to offer any useful advantage over reserpine in the treatment of hypertension.

Clinical investigations involving co-operation between hospital and family doctors have possibilities that should be explored further.

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MONOPLEGIA AND HORNER'S SYNDROME FROM PRESSURE PALSY

REPORT OF A CASE AND ANATOMICAL DISCUSSION

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Transient paralyses of the median and ulnar nerves sustained by prolonged pressure during narcotic-induced sleep, and particularly after bouts of acute alcoholism, are relatively commonly observed occurrences. Likewise, the condition of "Saturday night paralysis," involving the radial nerve in the upper part of the arm, is a well-known clinical entity. But, as Walshe (1958) points out, it is rare for the nerve of a healthy subject to sustain such pressure palsy, the majority of such patients being chronic alcoholics with an already debilitated peripheral nervous system.

The majority of brachial-plexus-pressure palsies reported in the literature are cases sustained during anaesthesia. Wood-Smith (1952) describes a lesion of C 5 and C 6 roots sustained during operation, and cases are also reported by Raffan (1950), Shaw (1953), and Westin (1954). The *Lancet* (1950) had a leading article on this subject; and, in particular, the hazards of the Trendelenburg position have been well covered. Ewing (1950) stressed the mechanism of abduction of the arm in the Trendelenburg position, causing traction injuries. Traction was incriminated also in the earlier series of Clausen (1942). Kiloh (1950) felt that both traction and pressure were of significance. But reports of cases arising apart from operative anaesthetic hazard are few and far between; the case of "pack palsy" reported by Bom (1953) in the Korean war is a rarity.

The occurrence, therefore, of an extensive lesion of the cervical and brachial plexus due to direct pressure